

PCT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

POSTNER, Marya, A.
Cooley Godward LLP
3000 El Camino Real
Five Palo Alto Square
Palo Alto, CA 94306-2155
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 24 March 2000 (24.03.00)	
Applicant's or agent's file reference NAVI009/02WO	IMPORTANT NOTIFICATION
International application No. PCT/US99/21151	International filing date (day/month/year) 14 September 1999 (14.09.99)
International publication date (day/month/year) 23 March 2000 (23.03.00)	Priority date (day/month/year) 14 September 1998 (14.09.98)
Applicant NAVICYTE, INC. et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
14 Sept 1998 (14.09.98)	60/100,290	US	09 Nove 1999 (09.11.99)
14 Sept 1998 (14.09.98)	60/100,224	US	09 Nove 1999 (09.11.99)
18 Nove 1998 (18.11.98)	60/109,232	US	09 Nove 1999 (09.11.99)
18 Nove 1998 (18.11.98)	60/109,234	US	11 Nove 1999 (11.11.99)
26 May 1999 (26.05.99)	09/320,372	US	22 Marc 2000 (22.03.00)
26 May 1999 (26.05.99)	09/320,270	US	09 Nove 1999 (09.11.99)
26 May 1999 (26.05.99)	09/320,371	US	22 Marc 2000 (22.03.00)
26 May 1999 (26.05.99)	09/320,545	US	09 Nove 1999 (09.11.99)
26 May 1999 (26.05.99)	09/320,544	US	09 Nove 1999 (09.11.99)
26 May 1999 (26.05.99)	09/320,069	US	04 Nove 1999 (04.11.99)

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>R. Raissi</p> <p>Telephone No. (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 10 January 2001 (10.01.01)	
International application No. PCT/US99/21151	Applicant's or agent's file reference NAVI009/02WO
International filing date (day/month/year) 14 September 1999 (14.09.99)	Priority date (day/month/year) 14 September 1998 (14.09.98)
Applicant GRASS, George, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 13 April 2000 (13.04.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
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CONFIDENTIAL

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing (day/month/year) 04 FEB 2000

Applicant's or agent's file reference
NAVI009/02WO

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US99/21151

International filing date
(day/month/year) 14 SEPTEMBER 1999

Applicant
NAVICYTE INC.

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

- 4. Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Form PCT/ISA/220 (January 1994)☆

DIR: 04 APR 00
 HQ: 04 APR 00

bound by Chapter II.
 NHU-010/p6 US
 NHU-010/p5 US
 NHU-010/p4 US
 NHU-010/p3 US
 Authorized officer

NAVI-010/02US
NAVI-001/02US
file 175 n: lutt.
Sentinel
(703) 308-0196

DUE: 04 MAR 00
FOL: 04 MAR 00

(See notes on accompanying sheet)

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NAVI009/02WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US99/21151	International filing date (day/month/year) 14 SEPTEMBER 1999	(Earliest) Priority Date (day/month/year) 14 SEPTEMBER 1998
Applicant NAVICYTE INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (See Box I).
2. ☐ Unity of invention is lacking (See Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ transcribed by this Authority.
4. With regard to the title, ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. _____ ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21151

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 18
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21151

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G06F 19/00; C12Q 1/00

US CL : 435/4, DIGEST 2; 702/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4, DIGEST 2; 702/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/19359 A1 (CARELL et al) 20 July 1995, see the entire abstract.	1-17
Y	US 5,789,160 A (EATON et al) 04 August 1998, see the entire document, especially the West search report last paragraph attached to patent.	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 19 DECEMBER 1999	Date of mailing of the international search report 04 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH W. RICIGLIANO Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21151

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1-17 Y	US 5,770,384 A (ANDROPHY et al) 23 June 1998, see the entire document, especially the attached WEST data base search.	1-17
Y	HARVEY STEWART, C. 'Drug Absorption, Action and Disposition.' In Remington's Pharmaceutical Sciences. Easton, Pennsylvania: Mack Publishing Co., 1990, p 697-724, see also the attached chapters on pharmacokinetics spanning p. 725-756.	1-17
Y	ROSSUM et al. 'Pharmacokinetics: a dynamic systems approach.' In: Drug Metabolism and Distribution. Edited by John W. Lamble. Amsterdam: Elsevier Press, p. 159-167.	1-17
Y	GEX-FABRY et al. 'Considerations on data analysis using computer methods and currently available software for personal computers.' In: Pharmacokinetics of Drugs. Edited by Peter G. Welling et al. Berlin: Springer-Verlag 1994, p 507-527.	1-17
Y		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21151

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST- USPAT and DERWENT FILES, DIALOG, NCBI and NLM sites
library, combinatorial, pharmacokinetics, pharmacodynamics, gastrointestinal, absorption, bioavailability, compartments,
Prophet, Drugmodel, Stella, PCNONLIN, computer, microcomputer. LANGRAN

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Claim 18 is directed to a library produced by the method of claims 1, 3, 6 or 16. However, these are screening methods which provide an inadequate written description of the claimed library because no structural limitations on the members are provided. As such it is not possible to determine what would or would not be encompassed by the claimed libraries or to search them.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 19 DEC 2000

WIPO

PCT

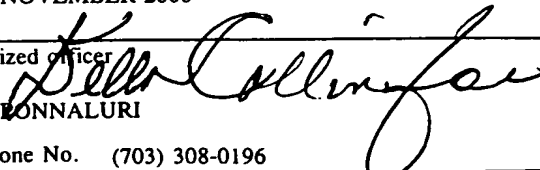
Applicant's or agent's file reference NAVI009/02WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/21151	International filing date (day/month/year) 14 SEPTEMBER 1999	Priority date (day/month/year) 14 SEPTEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): G06F 19/00; C12Q 1/00; C07B 1/00L and US Cl.: 435/4, DIGEST 2; 702/19		
Applicant NAVICYTE INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 13 APRIL 2000	Date of completion of this report 26 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  P. KONNALURI
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21151

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:

pages 1-127, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the claims:

pages 128-131, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the drawings:

pages 1-36, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/21151

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 18

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 18 are so unclear that no meaningful opinion could be formed (*specify*).

Claim 18 is directed to a library produced by the methods of claims 1, 3, 6 or 16. However, these are screening methods which provide an inadequate written description of the claimed library because no structural limitation on the members are provided. As such it is not possible to determine what would, or would not, be encompassed by the claims

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/21151

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-17</u>	YES
	Claims <u>none</u>	NO
Inventive Step (IS)	Claims <u>none</u>	YES
	Claims <u>1-17</u>	NO
Industrial Applicability (IA)	Claims <u>1-17</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1, 3, 4, 6, 7 and 13 lacks an inventive step under PCT Article 33(3) as being obvious over US 5,770,384 and WO 9519359 and US 5,789,160 in view of Harvey.

US 5,770,384 teaches the screening of compounds to modulate the activity of a biological system (the E2-binding protein system) in vivo. The tests include cell free, cell based and whole animal systems for screening activity, cytotoxicity, bioavailability and other pharmacological parameters (col. 48 line 59-col. 49, line 5).

WO 9519359 teaches that combinatorial libraries can be used to prepare molecules with improved characteristics such as improved metabolic stability and absorption.

US 5,789,160 teaches that screening process end points in the combinatorial arts include: IC50 values, rates of inactivation, toxicity profiles, bioavailability, pharmacokinetics etc. (see col. 20, lines 15-27).

Harvey teaches that drug absorption is one of the pharmacokinetic parameters that influence the bioavailability of drugs. Harvey also teaches that different routes of administration have different availability profiles. Harvey et al also teaches the administration by gastrointestinal routes (oral and rectal) as well as parenteral administration are known. See "Absorption of Drugs" starting on page 711.

The references do not teach establishing a secondary library based upon the results of the absorption screening.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to prepare a secondary library of molecules with the appropriate absorption characteristics when conducting a screen as taught by the references as combined, as the purpose of conducting a screening assay is to separate those member compounds having desired characteristics from those that do not. One of ordinary skill in the art would have been motivated to do so in order to prepare compounds with improved absorption characteristics (relative to the route of administration), which the references teach are desirable to obtain. One of ordinary skill in the art would have reasonably expected to be successful in forming a library based upon those members with desired absorption characteristics as (Continued on Supplemental Sheet.)

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

absorption and other pharmacological parameter have routinely been the basis of pharmacological screening as evidenced by the references cited.

Claim 1-17 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Holsford et al and Gex-Fabry and Rossum

The references as combined above do not teach the use of computer implemented pharmacokinetics tools or that such tools may use differential equations in forming the descriptions of the systems under study.

Holsford et al. teach the "DRUGMODEL" program implemented on the PHROPHET computer system for pharmacokinetic analysis. The program is used for several purposes including the analysis of multicompartment pharmacokinetic models. This reference does not state if the system uses the integrated forms of the equations for calculating the outcomes or the differential forms.

Gex-Fabry, similar to Holsford et al teach computer software for compartment models of pharmacokinetic problems (see pg 509 for example).

Rossum et al teach that pharmacokinetics can be approached from the dynamics approach whereby one uses the differential equations to develop drug kinetics in tissues and organ subsystems. Each of these systems is a compartment where the level of drug can be represented by the rate of input and output (including metabolism).

It would have been prima facie obvious to one of ordinary skill in the art to use computer implemented pharmacokinetics tools as taught by Holsford et al and Gex-Fabry, including those which used dynamic calculations based on differential rate equations as taught by Rossum et al in the screening methods as taught by the references as combined, supra, because computer implemented pharmacokinetics tools were well-established in the art at the time the invention was made. One of ordinary skill in the art would have been motivated to do so because the computer implemented tools can rapidly and accurately handle complex calculations. One of ordinary skill in the art would have reasonably expected to be successful because the references as combined teach that pharmacokinetics tools were established and had previously been successfully used in pharmacokinetic analysis.

Claims 1-17 lack novelty step, inventive step for the reasons of the record.

----- NEW CITATIONS -----

HOLFORD, N.H.G. "DRUGMODEL" In "Proceedings of the fifth annual symposium on computer applications in medical care." New York IEEE, 1981, pages 603-606.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21151

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G06F 19/00; C12Q 1/00

US CL : 435/4, DIGEST 2; 702/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4, DIGEST 2; 702/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/19359 A1 (CARELL et al) 20 July 1995, see the entire abstract.	1-17
Y	US 5,789,160 A (EATON et al) 04 August 1998, see the entire document, especially the West search report last paragraph attached to patent.	

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 DECEMBER 1999

Date of mailing of the international search report

04 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JOSEPH W. RICIGLIANO

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21151

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1-17 Y	US 5,770,384 A (ANDROPHY et al) 23 June 1998, see the entire document, especially the attached WEST data base search.	1-17
Y	HAF JEY STEWART, C. 'Drug Absorption, Action and Disposition.' In Remington's Pharmaceutical Sciences. Easton, Pennsylvania: Mack Publishing Co., 1990, p 697-724, see also the attached chapters on pharmacokinetics spanning p. 725-756.	1-17
Y	ROSSUM et al. 'Pharmacokinetics: a dynamic systems approach.' In: Drug Metabolism and Distribution. Edited by John W. Lambie. Amsterdam: Elsevier Press, p. 159-167.	1-17
Y	GEX-FABRY et al. 'Considerations on data analysis using computer methods and currently available software for personal computers.' In: Pharmacokinetics of Drugs. Edited by Peter G. Welling et al. Berlin: Springer-Verlag 1994, p 507-527.	1-17
Y		

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 18
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST- USPAT and DERWENT FILES, DIALOG, NCBI and NLM sites
library, combinatorial, pharmacokinetics, pharmacodynamics, gastrointestinal, absorption, bioavailability, compartments,
Prophet, Drugmodel, Stella, PCNONLIN, computer, microcomputer. LANGRAN

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Claim 18 is directed to a library produced by the method of claims 1, 3, 6 or 16. However, these are screening methods which provide an inadequate written description of the claimed library because no structural limitations on the members are provided. As such it is not possible to determine what would or would not be encompassed by the claimed libraries or to search them.